a set of independent risk factors. The key findings, relative risks and 95% confidence intervals were calculated and are presented below.

Results:

Risk factors at baseline (RR for)	Univariate RR	Multivariate RR
Age, years, 1 extra year	1.04 (1.02,1.05)	1.03 (1.01, 1.06)
Diabetes, Yes/No	2.35 (1.56, 2.35)	2.13 (1.32, 3.46)
Treatment for rejections, Yes/No	1.47 (1.00, 2.16)	1.5(1.01, 2.48)
Coronary heart disease, Yes/No	3.28 (2.08, 5.18)	2.11 (1.23, 3.62)
Total cholesterol, (1 extra mmol/L)	1.31 (1.12, 1.55)	1.21 (0.97, 1.50)
LDL cholesterol (1 extra mmol/L)	1.41 (1.18, 1.69)	1.34 (1.09, 1.66)
HDL Cholesterol (1extra mmol/L)	0.55 (0.34, 0.90)	0.56 (0.31, 1.02)
Triglycerides (1extra mmol/L)	1.11 (1.03, 1.19)	
ST-T abnromalities, Yes/No	2.02 (1.32, 3.08)	
Pulse Pressure (1 extra mmHg)	1.01 (1.00, 1.02)	
Serum creatinine (10 extra umol/L)	1.05 (1.02, 1.08	1.05 (1.01, 1.09)
Aspirine use, Yes/No	1.65 (1.08, 2.54)	

Conclusion. The data demonstrate that in renal transplant patients traditional risk factors such as age, diabetes, previous coronary heart disease and lipid values are major determinants of cardiac risk. The analysis also demonstrates that renal function and rejection episodes are independent risk factors for cardiac events.

1124-192 Rosiglitazone Reduces Novel Biomarkers of Cardiovascular Disease in Subjects With Type 2 Diabetes Mellitus Already on Statin Therapy

John D. Brunzell, Santica Marcovina, Dahong Yu, Alexander Cobitz, Errol Gould, Hongzi Chen, Lisa Porter, University of Washington, Seattle, WA, GlaxoSmithKline, King of Prussia, PA

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in type 2 diabetes (T2DM). Increased preponderance of small dense LDL particles and decreased HDL are atherogenic factors associated with insulin resistance (IR) and the metabolic syndrome. IR is also associated with hypercoagulable and proinflammatory states which increase CVD risk. In T2DM, treatment with rosiglitazone (RSG) has demonstrated conversion of the small dense LDL Type B phenotype (LDL Rf < 0.263) to the less atherogenic Type A phenotype (LDL Rf ≥ 0.263) as well as improvement in concentrations of additional CVD biomarkers including CRP, PAI-1 and MMP-9. The effect of RSG on CVD risks factors in T2DM subjects on statin therapy with predominately small dense LDL was evaluated. Seventy two subjects on diet/exercise, or metformin monotherapy, who had received at least 8 weeks of statin therapy, and had LDL Rf < 0.263 were randomized to the addition of placebo (N=14) or RSG 4mg (N=29) or 8mg (N=29) TDD. **Results**: By study end (Week 12), 24% (4mg) and 36% (8mg) of patients on RSG had converted to a pattern of predominately large, buoyant LDL Rf (LDL Rf ≥ 0.263) compared to no conversion in the placebo group. Significant reductions in CRP and PAI-1 were observed in RSG treated subjects.

	Placebo N=14	RSG 4 mg N=29	RSG 8 mg N=29
% patients converted to LDL Rf ≥ 0.263 (%)	0	23.5	36*
Mean Δ & %Δ (95% ci) from baseline:			
LDL Rf	-0.0003 (-0.0112, 0.0107)	0.011* (0.0033, 0.0187)	0.014* (0.0069, 0.0212)
CRP (%)	17.26 (-18.41, 68.50)	-35.38* (-49.67, -17.05)	-39.08* (-52.36, -22.10)
PAI-1 antigen (%)	-22.69 (-42.12, 3.28)	-10.63 (-26.81, 9.13)	-22.65* (-37.05, -4.96)
PAI-1 activity (%)	-29.02 (-57.08, 17.38)	-17.30 (-41.45, 16.83)	-30.72* (-51.14, -1.76)
MMP-9 (%)	20.13 (-14.59, 68.97)	-8.70 (-27.39, 14.79)	-17.76 (-34.44, 3.17)

* Statisticallysignificant

Conclusion: In T2DM subjects on statins, RSG significantly increased LDL particle size and reduced CRP and PAI-1, suggesting RSG may reduce CVD events.

1124-193 Dose of Fish Oil Needed to Achieve Cardioprotective Blood Levels of Omega-3 Fatty Acids

William S. Harris, Mid America Heart Institute, Kansas City, MO, University of Missouri-Kansas City, Kansas City, MO

Background: The evidence for a cardioprotective effect of omega-3 fatty acids (FA) has accumulated to the point where the American Heart Association (AHA) now recommends that patients with known coronary heart disease (CHD) consume about 1 g/d of eicosapentaenoic and docosahexaenoic acids (EPA+DHA), and adults without disease should eat at least two (preferably oily) fish meals per week. (The latter would provide about 500 mg/d EPA+DHA). Both epidemiological and interventional studies suggest that these intakes will lower risk for death from CHD by 30%-50%. A variety of studies point to a red blood cell (RBC) EPA+DHA level (hereafter, called the Omega-3 Index) of >=8% (percent of total RBC FA) as a reasonable target value for cardioprotection. An Index of <=4% is associated with relatively high risk. This study was undertaken to determine the effects of AHA-recommended intakes of omega-3 FA from supplements on the Omega-3 Index.
Methods: Healthy subjects on stable background diets were randomized to supplementation with either 0 (placebo; n=22), 0.5 g (n=24), or 1.0 g (n=10) of EPA+DHA (ROPUFA-30, Roche Vitamins). After five months, their Omega-3 Indexes were determined. Compliance was determined by capsule count.
Results: Overall compliance was 95%, and it was not less than 75% for any subject. The mean (SD) Omega-3 Indexes achieved were 4.3 (1.2%), 8.0 (1.7%), and 10.0 (2.8%), respectively. Omega-3 Indexes of >=8% were achieved by 5%, 54%, and 80% of those taking 0, 0.5g and 1.0 g/d, respectively. Indexes of <=4% were observed in 55%, 4% and 10% in each respective group.
Conclusions: These results suggest that most people taking 1 g EPA+DHA/d will achieve or surpass the 8% target value for the Omega-3 Index, and that about half of those taking 500 mg/d will reach the 8% level. Thus, based upon blood levels likely achieved, AHA recommended intakes should produce significant cardioprotection. The Omega-3 Index identifies a risk factor that is easily, safely and inexpensively corrected and may represent a novel, physiologically-relevant, independent and graded marker of risk for death from CHD. (Sponsored in part by Roche Vitamins, Inc.).

1124-194 Metabolic Syndrome and Prevention of Premature Coronary Artery Disease

Ana Mari Schaper, Kwame Osei Akosah, Vicki Lynn McHugh, Sharon Ione Barnhart, Patricia A. Perlock, Troy Haider, Michelle Ann Mathiason, Gundersen Lutheran Health System, La Crosse, WI

Background: Metabolic Syndrome (MS) and primary prevention of coronary artery disease (CAD) is becoming increasingly appreciated. The National Cholesterol Education Program (NCEP III) guidelines have defined MS and recommended aggressive management. Consequently, an emphasis needs to be placed on the identification of persons with MS. Lipoprotein subclass analysis allows for determination of atherogenic lipoprotein traits (ALT) of MS, but its incremental value remains unknown.
Objective: To determine the rate of MS in subjects screened for primary prevention and to assess incremental value of ALT.
Methods: 254 young adults (women ≤ age 65; men ≤ 55) without known CAD, scheduled for elective coronary angiogram had labs drawn for lipid and lipoprotein analysis (LipoScience, Inc). MS per NCEP III was defined as the presence of ≥3 of the following traits: low HDL (men <40 mg/dL; women <50 mg/dL), high triglyceride (≥ 150 mg/dL), hypertension (≥130/85 mm Hg), fasting glucose (≥ 110 mg/dL), and BMI ≥30. ALT was defined as ≥2 of the following values determined by nuclear magnetic resonance spectroscopy (NMR): small LDL pattern B (≤ 20.5 nm), reduced large HDL (<11 mg/dL) and elevated large VLDL (>27 mg/dL). CAD was defined as stenosis severity of ≥ 50%
Results: Mean age was 53±8. 82% were overweight or obese. The mean total, LDL, and HDL cholesterol levels were acceptable per NCEP III and not statistically different between subjects with and without CAD. Mean triglyceride (170 versus 138 mg/dL, p=0.002) and glucose (139 versus 109 mg/dL, p=0.005) were higher in those with CAD. MS was present in 59 (24%) of participants. ALT was present in 85 (35%) of participants. 73 participants met criteria for CAD, of whom 26 (36%) had MS, and 35 (48%) had ALT. The odds for MS in predicting CAD were 2.3 (CI: 1.3-4.2, p=0.006). The odds for ALT were 2.2 (CI: 1.2-3.9, p=0.007). Using either criterion, as many as 43 (59%) of subjects with CAD were identified (OR=2.6, CI: 1.5-4.5, p<0.001).
Conclusion: In a population of young adults with high levels of obesity and elevated triglyceride, the use of both of these definitions provides incremental value in identifying high-risk young adults who should be targeted for aggressive risk modification.

1124-195 Anthropomorphic Predictors of Insulin Sensitivity in a Healthy Population

Justo Sierra Johnson, Bruce D. Johnson, Kent R. Bailey, Stephen T. Turner, Mayo Clinic, Rochester, MN

Background: Insulin sensitivity (S_I) is the capability of insulin to increase glucose disposal. Abdominal fat distribution has been associated with insulin sensitivity. However, it is not clear whether sophisticated measures (DEXA scanning) of body fat and fat distribution are better predictors of S_I than simple measures (BMI, waist and hip circumferance, waist-to-hip ratioWHR). *Methods:* We studied 256 healthy Caucasian subjects from Rochester, MN (age 19-60, 133 women) who were admitted to the GCRC for measurement of S_I using the minimal model technique. All subjects had the simple and the sophisticated measures of body fat distribution taken. Body fat measures were analyzed and compared individually (controlling for age and gender) and in multiple regression models, in relation to S_I. *Results:* Among simple measures: waist circumferance and BMI had the best correlations with S_I (see Table), while the corresponding best predictors among the DEXA measures were: head fat (raw and percent) and upper body fat. When WHR and BMI were combined, or when head fat and upper body fat were combined, the

R^2 increased to 0.44 (P<0.05). Finally, a model which included WHR, Head fat, and Upper Body fat yielded a maximal R^2 of 0.47 (P<0.05), an improvement over either set of measurements alone. *Conclusion:* Simple measures when used alone are as effective as more sophisticated methods like DEXA for predicting S_I in a healthy population. However, when these measures are combined there is a small increased predictive power.

Table. Best 'Univariate' Predictors of Insulin Sensitivity

Parameter	Estimate	t Ratio	Pr > t	R^2
Weight (kg)	-0.020	-11.47	<0.0001	0.37
BMI	-0.062	-12.77	<0.0001	0.40
Head % Fat	-0.040	-12.52	<0.0001	0.41
Upper Body Fat (kg)	-0.044	-12.50	<0.0001	0.41
Head Fat (kg)	-0.807	-12.78	<0.0001	0.42
Waist (cm)	-0.028	-13.38	<0.0001	0.42

* Age and gender were forced into every model.

1124-196 **Impact of Elevated Age and Sex-Adjusted Body Mass Index in School Age Children on Insulin Resistance and Lipoprotein Subfractions**

David K. Murdock, Karen Olson, Kirk Jenkins, Mary Roth, Sharon Fox, Patrick Hughes, Bryan Hendricks, Cardiovascular Research and Education Foundation, Inc, Wausau, WI, Community Health Care/Wausau Health Foundation, Wausau, WI

Background: The Wausau SCHOOL Project is a community-based effort to assess the frequency of cardiovascular risk factors in students in the Wausau School District. **Objective:** Define the incidence of elevated BMI and determine its relationship to standard lipid profiles, homeostatic model assessment of insulin resistance (HOMA-IR), LDL particle size and number. **Methods:** Age and sex adjusted BMI (zBMI), fasting plasma insulin, glucose levels and nuclear magnetic resonance lipid profiles (LipoScience®) was measured in 225 randomly selected students (110 in 2nd grade and 125 in 11th grade). Overweight was defined as zBMI > 85th centile based on 2000 CDC norms. **Results:** Over 31% of the students were classified as overweight. (30.6% in 2nd grade and 32.5% in 11th grade). HOMA-IR values were significantly higher for 11th graders than for 2nd graders (2.18±2.65 vs. 1.22± 1.07, p<0.01). HOMA-IR values were also significantly higher for females than for males (2.04±2.66 vs. 1.33±0.94, p<0.05). Those with zBMI above the 85th centile had significantly higher levels of total cholesterol (182.0±34.0 vs. 170.2±28.5, p<0.01), LDL (123.4±28.5 vs. 112.7±25.7, p<0.01), triglycerides (118.6±80.7 vs. 86.4±35.6, p<0.001), LDL particle number (1299.8±379.5 vs. 1135±248.0, p<0.001), and HOMA-IR (2.61±3.47 vs. 1.32±0.09, p< 0.001), while HDL levels were lower (43.7±10.0 vs. 47.5 ±9.7, p<0.01). There were no significant differences in LDL particle size. **Conclusions:** A significant percentage of children and adolescents are overweight. IR increases significantly with age and zBMI and is associated with an atherogenic lipid profile characterized by an increase in the number of small LDL particles and TG levels and lower HDL levels, similar to that seen in adults.

1124-197 **Additive Gene-Gene Interaction Between CYP7A1 and Apolipoprotein E as Genetic Determinants of Low-Density Lipoprotein Cholesterol-Lowering Response to Atorvastatin**

Kouji Kajinami, Noboru Takekoshi, Margaret E. Brousseau, Jose M. Ordovas, Ernst J. Schaefer, Kanazawa Medical University, Uchinada, Japan, Tufts University, Boston, MA

Background: The mechanisms responsible for interindividual variation in response to statin therapy remain uncertain. Bile acid biosynthesis is one of the determinants of intracellular cholesterol and, in turn, cholesterol synthesis rate in hepatocytes. This raises the hypothesis that variation in the cholesterol 7α-hydroxylase gene (*CYP7A1)*, a key enzyme in bile acid biosynthesis, may influence the statin response. *Methods and Results:*To test this hypothesis, we examined a promoter polymorphism (A–290C) in *CYP7A1* in 324 hypercholesterolemic patients treated with atorvastatin 10mg. The *CYP7A1* polymorphism was significantly and independently associated with poor LDL cholesterol response. Mean reductions were -39% in wild type allele homozygotes, -37% in variant allele heterozygotes, and -34% in variant allele homozygotes, respectively (p<0.0001 for linear trend). The effects of this polymorphism were more striking in men than in women and were enhanced by the coexistence of common variants of the apolipoprotein E gene (*APOE*), ε2 or ε4. In subjects having wild type alleles at both loci, the mean reduction in LDL cholesterol was -40%, while in subjects having two *CYP7A1* variant alleles and at least one variant *APOE* allele, the mean reduction in LDL cholesterol was -31% (p<0.0001). In addition, combination analysis of these two polymorphsims more accurately predicted the achievement of goal LDL cholesterol, than did both single polymorphism analysis. *Conclusions:*The *CYP7A1* A–290C promoter variant was significantly and independently associated with poor response to atorvastatin. The effects of this polymorphism were additively enhanced, when common variants in another locus, *APOE*, coexist.

1124-198 **Plasma Sphingomyelin Levels in Coronary Artery Disease: A Relationship With Serum Triglyceride and Apolipoprotein B and Other Risk Factors**

Axel Schlitt, Stefan Blankenberg, Daoguang Yan, Hans von Gyzicki, Christoph Bickel, Karl Lackner, Juergen Meyer, Hans J. Rupprecht, Xian-Cheng Jiang, State University of New York, Downstate Medical Center, Brooklyn, NY, Johannes Gutenberg University, Mainz, Germany

Objective
Sphingomyelin (SM) is one of the major phospholipids in the cell membrane and in lipoproteins. In human plasma, SM is mainly found in atherogenic lipoproteins, thus, high levels of SM may promote atherogenesis.
Methods
To further evaluate the role of SM in atherosclerosis, we measured plasma SM levels in 1,102 patients with coronary artery disease (CAD) and 444 healthy controls.
Results
We demonstrated that plasma SM in CAD patients was significantly higher than in controls (51.8 versus 44.9 mg/dl; p < 0.001). Logistic regression analysis showed that plasma SM was significantly associated with incidence of CAD (OR: 4.9, 95% CI 3.4 – 7.0, for subjects in the fourth quartile in comparison to subjects in the first quartile). Plasma SM levels showed a strongest and significant correlation with plasma apolipoprotein B (apoB)- (r=0.34, p < 0.001) and triglycerides -levels (r=0.31, p < 0.001) in all subjects, respectively. The association between SM and incidence of CAD remained independently significant after adjustment for most potential confounders including apoB and triglyceride, such that patients within the fourth quartile of SM revealed a 6.0 fold (95% CI 3.4 – 7.0) increase of risk.
Conclusion
These results reveal that the proatherogenic potency of human plasma SM levels, as shown in this study by significantly elevated levels of SM in patients, could be related to abnormal apoB -containing or triglyceride -rich lipoprotein metabolism.

ORAL CONTRIBUTIONS

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Biology of Atherosclerosis: Inflammation and Plaque Instability

Tuesday, March 09, 2004, 10:30 a.m.-Noon
Morial Convention Center, Room 217

10:30 a.m.

841-1 **Ceramide Triggers Weibel-Palade Body Exocytosis**

Rinky Bhatia, Kenji Matsushita, Munekazu Yamakuchi, Craig Morrell, Charles J. Lowenstein, Johns Hopkins University School of Medicine, Baltimore, MD

Background: The sphingolipid ceramide mediates a variety of stress responses, including vascular inflammation and thrombosis. Activated endothelial cells release Weibel-Palade bodies, granules containing vWF and P-selectin, which induce leukocyte rolling and platelet adhesion and aggregation. We hypothesized that ceramide induces vascular inflammation and thrombosis in part by triggering Weibel-Palade body exocytosis.
Methods: We added ceramide to human aortic endothelial cells (HAEC) and assayed Weibel-Palade body exocytosis by measuring the concentration of vWF released into the media.
Results: Exogenous ceramide induces vWF release from endothelial cells in a dose-dependent manner. As little as 10 nM ceramide induces a 50% maximal release of vWF. Activators of endogenous ceramide production, neutral sphingomyelinase or tumor necrosis factor-a (TNF-a), also induce Weibel-Palade body exocytosis. We next studied the effects of nitric oxide (NO) on ceramide-induced Weibel-Palade body exocytosis, since NO can inhibit vascular inflammation. The NO donor S-nitroso-penicillamine (SNAP) decreases ceramide induced vWF release in a dose-dependent manner: the IC50% for SNAP inhibition of vWF release is < 1 uM. In contrast, the NOS inhibitor L-nitroarginine methyl ester (L-NAME) increases ceramide induced vWF release.
Conclusions: In summary, our findings show that endogenous ceramide triggers Weibel-Palade body exocytosis, and that endogenous NO inhibits ceramide induced exocytosis. These data suggest a novel mechanism by which ceramide induces vascular inflammation and thrombosis.

10:45 a.m.

841-2 **Periadventitial Fat Inflammation Correlates With Plaque Inflammation in Patients With Coronary Plaque Ruptures: New Marker of Plaque Vulnerability?**

Deborah Vela, Allen Burke, Alireza Zarrabi, Morteza Naghavi, Mohammad Madjid, Ward Casscells, III, Renu Virmani, James T. Willerson, Silvio Litovsky, Texas Heart Institute, Houston, TX, Armed Forces Institute of Pathology, Washington, DC

Background. Previous work from our laboratory showed the presence of significant phagocytic activity in the aortic peri-adventitial fat of animal models of atherosclerosis (apoE-deficient mice and Watanabe rabbits). The macrophage activity is only mild in the aortic adventitial fat of wild-type mice and rabbits. In the present study we studied the adventitial fat of human coronary arteries in patients with plaque ruptures and contrasted them with those of patients with stable fibrocalcific plaques. We hypothesized that the macrophagic density would be much greater in the former.